REVIEW ARTICLE

Cubosomes: Recent Developments and Applications from a Global Perspective

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ABSTRACT

Liquid crystalline cubosomes are self-assembly of aqueous lipid and surfactant mixture. They are discrete and sub-micron in size. It is an innovative lipid-based nanosystem resembling well-known vesicular systems including niosomes and liposomes. Cubic phases incorporate lipophobic, amphiphilic and hydrophilic, components through the utilization of a rounded bi-continuous lipid bilayer and water channels. Cubosomes contain lipids such as phytantriol (PHYT) and glycerol monooleate (GMO) which are amphiphilic in nature that are diffused in water and structured in 3-D as a "honeycomb" structure with suitable stabilizer (Poloxamer 407). Cubosomes are generated by mostly two techniques i.e., top-down, bottom-up methods. UV spectrophotometer, X-ray scattering, transmission electron microscopy, and photon correlation spectroscopy are used to characterize and evaluate cubosomes. They are commonly used in the administration of oral, ophthalmic, transdermal, and chemotherapeutic drugs. The liquid crystalline phase and bicontinuous cubic form nanoparticles are thoroughly discussed in this paper. In the current review search criterion used parameters affecting cubosomes bi-continuous lipid bilayer by top-down and bottom-up methods mostly. The sources referred from peer-reviewed recognized journals. Keywords used as filters were cubosomes, amphiphilic lipids, top-down, bottom-up, bicontinuous, GMO, and phytantriol (PHYT). For the purpose of a comprehensive update literature review over a range (1976–2023) has been conducted on the recent developments cubosomes system.

Keywords: Cubosomes, Amphiphilic lipids, Top Down, Bottom Up, Bicontinuous, Monooleate, Phytantriol.

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INTRODUCTION

In 1980, Larsson coined term "Cubosomes" to describe cubic molecular crystallography that resembled liposomes.[1] Cubosomes are nanostructured, sub-micron-sized, discrete particles of cubic liquid crystalline phase. The fact that surfactant bilayers divide the enclosures of two different water zones is referred to as "bicontinuous" in this context. An important benefit is the ability to alter the curvature of membrane.[2] One-fourth portion of the solid may be liquid crystals. They have polar, non-polar components in their polymers, lipids, and surfactants, which makes them amphiphilic.[3] Additionally, they have the symmetry of solid cubic crystallography and are thick, optically isotropic, and equivalent to liquid crystalline materials.[4] The fracture of the cubic phase produces colloidal thermodynamically stable dispersions. Cubosomes contain mostly amphiphilic lipids (glycerol monooleate), that are dispersed in water with the aid of stabilizers (poloxamer 407) using high-energy dispersion techniques like sonication and homogenization. Cubosomes have a three-dimensional "honeycomb" form as shown in Figure 1. They resemble square dots and range 10 to 500 nm. They are also somewhat round.[5] Each dot in the X-ray scattering method denotes the presence of cubic phase-containing pores. Husson and Luzzati were the first to find it.[6] Depending on the substance, the drug molecules are combined with the polymer in a 1:1 or 2:1 ratio.

Since their first discovery in 1980, cubosomes, a form of vesicular drug delivery system, gain interest of the nanotechnology community.[7,8] At higher dilution levels, other liquid crystalline systems become micelles, whereas cubosomes are stable at all dilution levels. This is due to the cubic phase's relatively poor solubility in water, which is generated by lipids. Cubosomes were found to be more stable than liposomes. Additionally, liposomes may have drawbacks such as aqueous hydrolysis, sedimentation, and aggregation during storage, they cannot be sterilised in clinical settings

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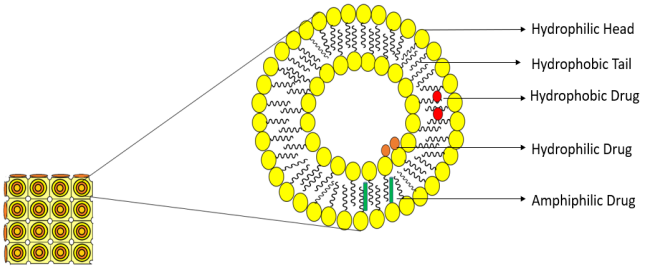


Figure 1: Cubosomes with various drug loading strategies displaying their interior & the cubic shape as well as membrane components

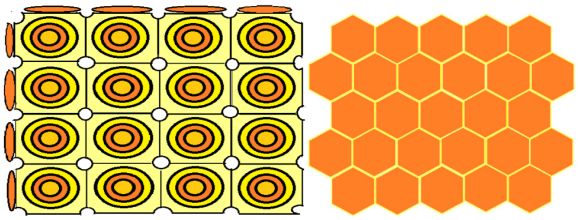


Figure 2: Honeycombed-shaped structure of cubosomes

use.[9] Despite being discovered in 1980, cubosomes are difficult to produce on large scale because of complex behavior and viscosity. Cubic phases have very high viscosities that are similar to those of solids because to their intriguing structure.[10] Larsson developed the name "cubosomes," which refers to the cubic molecular crystallography and liposome-like structure (Figure 2.).[1]

Advantages

- The method of preparation is easy
- Cubosomes are biocompatible, biodegradable & bioadhesive.
- They have longer thermodynamic stability.
- They can encapsulate compounds of all three types: hydrophilic, hydrophobic, and amphiphilic.
- Bioactive compounds are released in a modified manner.

Disadvantages

- Large-scale production is difficult because the cubic phase has such a high viscosity.[11,12]
- The entrapment efficiency of aqueous molecules is observed to be low.

Two fundamental theories have been proposed to elucidate the self-assembly mechanism of these surfactants into a distinctive configuration.

Opposing forces

The weak Van der Waals force (hydrogen bonds) is overcome by hydrophobic bonding when amphiphilic molecules are exposed to a polar solvent, as seen in the accompanying diagram (Figure 3).[13-15]

Packing parameter

The concept of packing parameter is the main determinant of aggregates that may form preferentially particular lipid.[16,17]

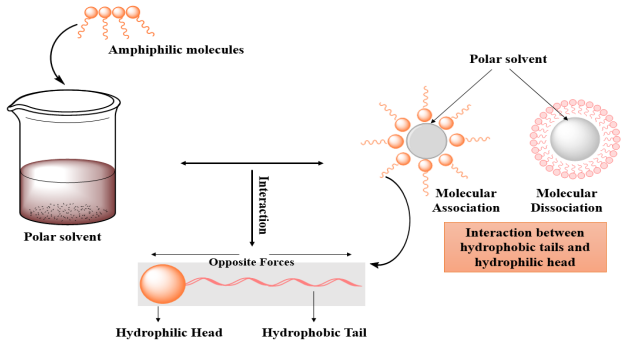


Figure 3: Amphiphilic molecules interaction

Israelachvilli *et al.*, in 1976 described the crucial packing parameter (P) which has further investigated by Abdelkader *et al.*, (Equation 1). It links a lipid's molecular form and characteristics to its preferred curvature to produce mesophase as depicted in Table 1.

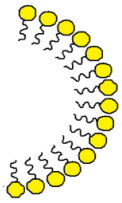
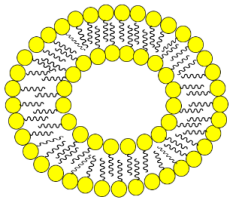
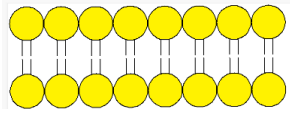
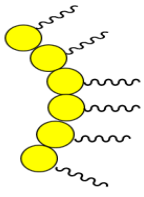
P = v/al (Equation 1)

(v) – volume, (l) - length hydrophobic chain, (a) - polar head surface area.

Shape and components

Cubosomes exhibit honeycombed structures varying in size from 10 to 500 nm. They have a spherical structure

Table 1: Shape and morphology of amphiphilic lipids that self-assemble in an aqueous environment

S. No.	*Curvature type*	*Packing parameter (P)*	*Morphology*
1)	Micelles (Curvature on chain)	v/al < 1	
2)	The closed lipid bilayer structure (Normal micelle structure)	1/2 > v/al > 1	
3)	Open lamellar structure (Zero curvature)	v/al = 1	
4)	Inverted micelles (Curvature occurs in the direction of the water)	v/al >1	

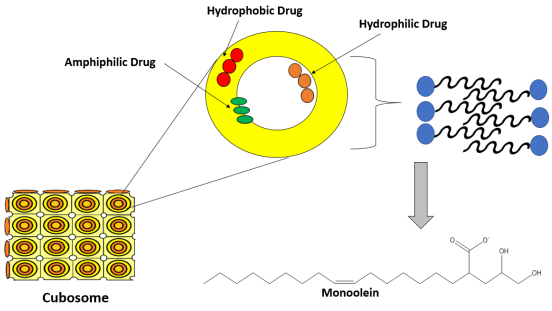


Figure 4: Cubosome components

that resemble as spherical dots (Figure 4). Dot indicates the existence of an aqueous cubic phase-containing pore. Simply said, cubosomes are liquid crystalline phase nanoparticles.[18]

Amphiphilic lipids

- *Glycerol*

Glyceryl monooleate (GMO), also known as monoolein, is the most often employed amphiphilic lipid in the formation of cubosomes.[19,20] GMO polar unsaturated monoglyceride with a melting point between 35 and 37°C, a storage temperature of 20°C, and 3 HLB value.[21] Monooleate synthetic combination of mainly glycerides ester of oleic that self-assemble produces bicontinuous cubic structures in water (Figure 5).[22]

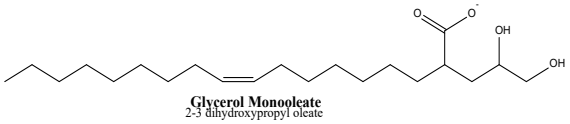


Figure 5: *Glycerol* monooleate

It was initially proposed in 1984 as a biocompatible encapsulating material, and today it is commonly utilised as an emulsifier.[23] It is non-toxic, biodegradable, and biocompatible, among other qualities.

Phytantriol

Phytantriol (PHYT), a common cosmetic component, has recently gained significant interest in the biomedical field because of its higher chemical stability than monoglycerides (absence of an ester group),[24,25] stronger skin penetration capabilities,[26,27] and improved moisture retention.[28] Liquid crystalline matrices based on PHYT have been demonstrated to be capable of sustaining release, particularly those with hydrophilic features, and are therefore regarded as a promising sustained drug delivery method.[29] Its increased stability after the addition of hydrophilic chemicals was approved by Rizwan *et al* (Figure 6).[30]

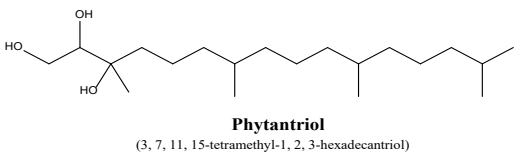


Figure 6: Phytantriol

Stabilizers

The most often used stabilizers are pluronics, (Poloxamer 407), known as the "gold standard" (Figure 7).[31,32] The hydrophilic (PPO) portion of F127 is meant to expand into the aqueous environment and stabilize the hydrophobic component of F127, which is meant to adhere to the cubosome surface.[13]

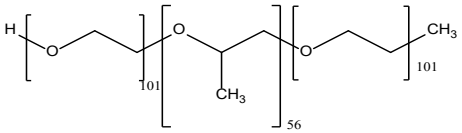


Figure 7: Pluronics

Cubosome precursors

Due to the high cost and difficulty of scaling-up high-energy processes so to prevent high-energy processing, precursors are needed. They can preserve thermosensitive drug molecules. The hydrotrope dilution technique produces cubosomes that are smaller and stable. The particles are created by nucleation, subsequently, they increase through saturation. Monoolein can be hydrolyzed in any hydrotrope to get this outcome. The mixture thereafter naturally precipitates or crystallizes after dilution.[33,34] This can be done without using a lot of shears. Cubosome preparations are simpler to scale up when using a liquid precursor method.[35,36] These are frequently discovered in mouthwashes and hand washes.

METHOD OF PREPARATION

The production of cubosomes nanoparticles is mostly done by top-down or bottom-up methods (Figure 5). Poloxamer 407 is a colloidal stabilizer required in both procedures to avoid cubosome dispersion aggregation.

Special Methods

- Bottom-up method
- Top-down method

Bottom-up method

This method produces cubosomes by dispersing liquid crystal-forming lipid, stabilizers, and hydrotropes in aqueous media with little energy input. The hydrotrope's main job is to break down lipids and keep the system viscous at high

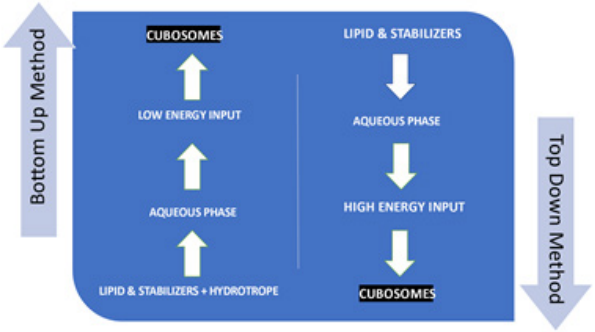


Figure 8: A diagrammatic representation of the methods for manufacturing cubosomes

concentrations.[37] This process is noticeably more effective in creating fine particles.

- *Advantages*
- It is a procedure that takes minimum time.
- Low energy input is required in this technique.
- It enables the use of temperature-sensitive materials.
- *Limitations*
- Because of the hydrotropes, it may induce allergic responses if taken orally.
- It may create milky white mixtures.

Top-down Method

The easiest method for creating cubosomes is this one. There are two stages to the top-down methodology. In order to prevent coagulation, the first step involves combining lipids with stabilizers to form cubic phase using high-energy methods. The rupture of the cubic phases necessitates a significant energy input.[38,39] By using this method, ribosomes are created that are nearly a year resistant to aggregation.

- *Advantages*
- Formulations that have been prepared are clear and visible.
- This approach doesn't involve the utilization of organic solvents.
- This methodology is relatively easy.
- *Limitations*
- In this technique large-scale manufacturing is limited due to its viscosity.
- High energy input it restricts the integration of temperature-sensitive components such as peptides and proteins.

Other Methods

Spray drying techniques

Starch and dextran-encapsulated monoolein precursors are produced using the spray drying technique. In this procedure, the monoolein is hydrated and then coated with polysaccharides (dextran/starch). After that, the polymers are blended to maintain stability.[40]

High shear application

In this process, stabilizers are utilized to stop particle aggregation. Although it's a great method, there are several disadvantages, one of which is the high-shear application.[41]

Probe ultra sonication

This method quick and used to prepare smaller volumes of samples. Even if the sample volume is 600 µL, it can be dispersed. The gels are formed by combining stabilizers in this procedure. After that, solvent equilibration occurs, resulting in cubic phase formation.[25]

Cubosome preparation via automation

This process has the potential to make a high number of cubosomes. In this approach of cubosome preparation, a probe sonicator and robotic equipment are utilized. The sonication is then carried out by a robot. The physicochemical qualities may be easily examined using this approach.[42]

High-pressure homogenization

The produced dispersion is homogenized in a high-pressure homogenizer. It can be used in large-scale sampling systems (30 mL). Temperature is a crucial factor in this step.[43-45]

Evaluation Parameters

Visual inspection

The external appearance is examined visually including opacity, color, and homogeneity.

Viscosity

Viscosity is determined with a viscometer, such as the Rotational Brookfield Viscometer.

Transmission electron microscopy

To check the appearance of the cubosomes, TEM can be performed. An electron microscope was used to capture the electron microphotographs.[46]

Zeta potential

The intensity of electrostatic repulsion with similar charges is represented by the zeta potential. It is an important measure of formulation stability.

Entrapment efficiency

Entrapment efficiency (EE) can be evaluated by the ultra-filtration method. In this method, the concentration of a medication that has been entrapped is determined using a spectrophotometer. De-ionized water must first be used to dilute the sample before centrifugation if necessary.[47]

Particle size

Photon correlation spectroscopy is used to determine particle size distributions of cubosomes. The polydispersity index and the z-average were calculated.[48-51]

X-ray scattering

The structural patterns in the sample can be assessed using small-angle scattering. It can detect the structure of molecules that are extremely small (5–25 nm).[24,41]

Stability study

Physical stability may be examined by analyzing organoleptic and morphological features throughout time. The aggregation, entrapment and medication content can be periodically to see if there is a likely change.[52-54]

Applications

Ocular applications

In 2011 Zaki *et al.*, studied that cubosomes have a prolonged retention in ocular surface and because of GMOs, they are said to increase the ocular bioavailability of loaded medications.[55] Also, Kaushika *et al.*, showed the effect of the development of cubosomes, adopted to combat various ocular diseases.[56] Cubosome formulation increases the permeability coefficient of loaded dexamethasone *via* excised rabbit corneas. Gan L *et al.* demonstrated the effect that cubosomes resulting in an increase in dexamethasone amount in compared to eye drops, in aqueous humor during a pharmacokinetic study.[57]

Dermatological application

In transdermal drug delivery, the topmost layer serves as a considerable barrier to absorb topically applied drugs.[58] On the other hand, because of their distinct structure and properties, cubosomes present a possible route for transdermal drug delivery. Due to the bioadhesive characteristics to stratum corneum as a result of GMO, cubosomes are utilised widely in the topical administration of medications.[4] Recently, cubosomes have been employed in a number of dermatological applications. T. Rattanapak, *et al.* reported in 2013 that transcutaneous immunisation (TCI) vaccine is a crucial dermatological usage. On the other hand, cubosomes

Table 2: Cubosomes applications

S. No.	*Drug*	*Type of application*	*Pharmacological uses*	*Conclusion*	*References*
1.	Ketorolac	Ocular	Seasonal allergies cause irritated eyes, which NSAIDs are used to alleviate.	Cubosomes enhance ketorolac transcorneal permeability and precorneal retention time.	69
2.	Timolol (TM)	Ocular	Treatment for glaucoma using a non-selective beta-blocker drug	In comparison to commercially available eye drops, timolol-loaded cubosomes had more corneal penetration, longer precorneal duration of action, and improved intraocular pressure-lowering efficacy.	70
3.	5-fluorouracil (5-FU)	Anticancer	Hepatocellular carcinoma and other advanced gastrointestinal malignancies are treated with antineoplastic drugs.	Cubosomes greatly enhance the 5-FU level in the liver by roughly 5-fold.	71
4.	Dexamethasone (DEX.)	Ocular	Anterior ocular inflammation therapy	DEX bioavailability and preocular retention time are improved when cubosomes are used.	57
5.	Flurbiprofen (FB)	Ocular	Inflammation of the eyes is treated with NSAIDs.	Cubosomes had less ocular discomfort and improvedtranscornealpenetration of FB.	55
6.	Capsaicin	Dermatological	Psoriasis, pruritus, and contact allergies are all treated with this drug.	Cubosomes produced sustained capsaicin release, prolonged retention with little skin irritation, and kept capsaicin stable under light and high temperatures.	57
7.	Indomethacin	Dermatological	Anti-inflammatory drug.	Cubosome depot action on the epidermis prolongs the anti-inflammatory efficacy of drug.	5
8.	Erythromycin	Dermatological	It is used to treat various forms of acne.	Cubosomes shown to be beneficial in treating and preventing acne by delivering erythromycin to the skin in a non-invasive and long-lasting way.	71
9.	Dapsone	Dermatological	Acne, systemic lupus erythematosus can all be treated with this antibiotic and anti-inflammatory drug.	Cubosomes enhance dapsone penetration compared to the commercial formulation.	46,72
10.	Insulin	Oral	Induced type 1 diabetic rats were treated	Cubosomes protected insulin from proteolysis, resulting in a more predictable and reproducible influence on hyperglycemia treatment.	62
11.	Ibuprofen	Oral	Analgesic non-steroidal anti-inflammatory medication.	Ibuprofen is released in a sustained release by cubosomes, resulting in a stable plasma level of ibuprofen and increased systemic bioavailability.	61
12.	Simvastatin	Oral	Uused to raise HDL and lower LDL, VLDL and lipids in the blood.	When given orally, cubosomes increased the bioavailability of the water-insoluble simvastatin.	64,73
13.	Dacarbazine	Anticancer	primary chemotherapeutic agents for melanoma.	The significant adverse effect of intravenous dacarbazine treatment is reduced by cubosome delivery. These physicochemical characteristics increase the shelf life, effectiveness, and safety of the loaded medication within cubosomes.	67,74
14.	Odorranalectin	Intranasal	Anti-Parkinson Drug	Coumarin relative absorption in the brain was around 3.46-fold higher than in untreated cubosomes.	48

and microneedles (MNs) have been used successfully in combination to deliver immunizations in skin. The cubosome-peptide preparation demonstrated greater skin durability and better aqueous peptide mixture penetration through the skin layers. As an outcome, researchers observed that transferring antigens to specific skin cells using a mix of MNs and cubosomes is a successful strategy.[59,60] Modified-release cubosomes containing methotrexate- through topical application in rheumatoid arthritis were developed by Kapoor *et al.* in 2020. MTX is still used as the "anchor drug" to treat RA. Novel medicinal drug delivery tools, such as MTX-Cubosomes, were created to improve delivery.

Oral applications

Cubosomes have also prompted attention for their potential application in oral medication administration for a variety of substances, including those that are poorly water-soluble, poorly absorbed, or have a high molecular size. Because of their bioadhesive qualities, and interactions with intestinal cell membranes, they aid in the absorption of orally delivered medicines.[61,62] In 2002 Chung *et al.*, reported more enhanced oral treatment of fasting streptozotocin-induced diabetic mice using insulin-loaded cubosomes.[63,64] They took additional precautions when making insulin-loaded cubosomes to maintain insulin activity. Their findings revealed that due to the bioadhesive properties of GMOs, cubosomes might offer sustained biocompatible oral administration of insulin with repeatable hypoglycemia impact and increased adsorption. Cubosome examples used through oral delivery are shown in Table 2.

Anticancer applications

The oral and topical administration of non-carcinogenic drugs is important for cubosome uses. Cubosomes were successfully employed for the targeted administration of non-carcinogenic medicines, with better pharmacokinetics parameters of the loaded pharmaceuticals.[65] 5-fluorouracil (5-FU) was successfully delivered to liver tissue using cubosomes. In vitro, the cubosome formulation showed a modified release profile, in first hour seeing a burst release of the medication and the following 4.5 hours seeing a more steady release of the remaining drug.[66,67] Additionally, the data showed a higher 5-FU amount in liver from the cubosomal formulation as compared to the solution form.

Intranasal application

The delivery of therapeutics in cubosomes form from nose to brain, eliminating the blood-brain barrier (BBB), has shown safe, beneficial method for central nervous system (CNS) problems. Wu *et al.* discovered a method of surface engineering PEGylated cubosomes with odorranalectin functional molecules. Using coumarin as a marker, the nose-to-brain distribution feature of odorrana lectin cubosomes was investigated, and its relative absorption in the brain was around 3.46-fold higher than in untreated cubosomes.[48] The study indicates that administering odorrana-lectin cubosomes might improve performance.

Intravenous application

Esposito *et al.* demonstrated the effectiveness of nanoparticulate delivery of antiparkinson bromocriptine (BC) drug, including monoolein cubosomes and NLCs. BC was demonstrated to be encapsulated by cubosomes and NLC with astounding efficiency[68]

Controlled and sustained-release application

It is the most common use of cubosomes discovered by scientists. Controlled and sustained drug release is possible due to tiny pore size (5–10 nm), cubic phase best possible for modified-release, solubility in hydrophilic, hydrophobic, and amphiphilic compounds, as well as their biodegradability by simple enzymes.[4]

Antiviral application

Monoglycerides, which are essential in the formation of cubosomes, have microbicidal properties. As a result, they need to explore to treat sexually transmitted diseases caused by both viruses and bacteria.[4]

CONCLUSION

Cubosomes are self-assembled liquid crystalline particles formed of amphiphilic lipids, specifically GMO and PHYT. Cubosomes varies from 5 to 10 nm size and potential for encapsulating including hydrophilic, lyophobic, and amphiphilic compounds as drug delivery vehicles. Ultrasonication high-pressure homogenization might used to manufacture cubosomes mainly by two methods: top-down or bottom-up techniques. The potential to shape cubosomes in use, during formulation, and during manufacturing provides a lot of scope for product development. Due to their exceptional characteristics, cubosomes can be supplied by intravenous, topical, intranasal, ophthalmic, and oral routes, among others. Cubosomes bioadhesiveness, which enables their application in topical and mucosal depositions for the delivery of diverse actives, is one of its most significant and distinctive characteristics. Because the cubosome technology is new and produces a lot, there is a lot of scope for research to create new formulations that are efficient for use in industry and commerce.

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AUTHORS CONTRIBUTIONS

All authors contributed equally

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